Docket No 63419 (52171)
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Wolfgang Ritcher, Lutz Weber

Application No.: 10/535,474 | Confirmation No.: 4298

Filed: November 28, 2003 | Art Unit: 1626

For: THIA-EPOTHILONE DERIVATIVES FOR THE TREATMENT OF CANCER | Examiner: Joseph R. Kosack

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF LUDGER WESSJOHANN,PH.D, UNDER 37 C.F.R. § 1.132

I, Prof. Dr. Ludger Wessjohann, declare as follows:

1. I am the Director of the department of Bioorganic Chemistry of the Leibniz Institute of Plant Biochemistry, Halle (Saale), Germany. My field of research and expertise is in the area of organic and bioorganic chemisrty. I am co-author of several publications relating to the synthesis of epothilone derivatives.

2. I have carefully studied the above-referenced application (the "Application") and the office action dated December 7, 2007 for the Application rejecting claims 12-23 as allegedly obvious. I have also carefully studied and understood the following references. a) K.C. Nicolaou, Frank Roschangar, and Dionisios Vourloumis, Chemical Biology of Epothilones, Angew. Chem. Int. Ed. 1998, 37, 2014-2045 ("Nicolaou"); and b) George A. Patani and Edmond J. LaVoie, Bioisosterism: A Rational Approach in Drug Design, Chem. Rev. 1996,96, 3147-3176 ("Patani").

3. The subject matter of the Application pertains to epothilone derivatives wherein the CO group at C5 has been replaced by a sulphur atom or an SO_2 group. These compounds show a similar range of activity against certain cancer cell lines (e.g. cell lines MCF-& and KB-31).

For the reasons laid out below, I must respectfully disagree with the USPTO that the claims of the invention are in any way obvious in view of art cited by the USPTO.

4. Patani discusses a series of benzophenone dicarboxylic acids as potential inhibitors of LTB_4 (column 1, page 3167). In Table 39 it is shown that the sulfur linked derivatives 82d to 82f show similar activity to the carbonyl derivative. From these findings, Patani concludes that that this portion of the molecule is not critically involved in LTB_4 receptor binding. (cf. "However, the lack of any significant difference in activity upon replacement of the carbonyl with either a thioester, a sulfoxide or a sulfone, which differ widely with respect to their polarities and hybridisation, suggests that this portion of the molecule is not critically involved in LTB_4 receptor binding.")

5. Patani clearly teaches that if, in a non-critical part of a molecule, CO is replaced by sulfur or SO_2, he would expect no significant change in the biological activity. On the other hand, if, in a part of a molecule which is relevant for the biological activity, CO is replaced by sulfur or SO_2, Patani would expect major changes in the biological activity.

6. Nicolaou teaches that a loss of activity was observed when the C5 ketone was reduced or when the C5 substituent was removed (Page 2040). This clearly shows, that the CO-moiety at the C5 position is of great importance for the activity of epothilone derivatives. Although Nicolaou fails to show any compound or activities of compounds with a reduced ketone in the C5 position, a person of ordinary skill would nevertheless determine that this position is essential for the biological activity of the compound, since there is no reason to question the information given in Nicolaou.

7. Therefore, if at C5 of an epothilone derivative, CO is replaced by sulfur or SO_2, a person of ordinary skill in the art would expect that this replacement will have a great influence on the biological activity of the corresponding derivative. Consequently, a person of ordinary skill in the art could not expect that the molecules of the present invention show similar activities when compared with compounds carrying a CO group at C5.

8. Moreover, due to the different binding angles and size the person skilled in the art would expect that the replacement of CO by sulfur or SO_2 has a great influence on the conformation of a macrocycle and therefore, the person skilled in the art would expect that this also has a great influence on the biological activity of the corresponding derivative. As is apparent from the data given in the enclosed declaration by Dr. Wolfgang Richter, this is not the case in the epothilone derivatives of the present invention.

9. In addition, it is to be noted that in a R-CO-R molecule, all groups lie within one plane; whereas in a R-SO_2-R molecule, the oxygen is positioned above and below the plane created by the R-S-R group. Therefore, a person of ordinary skill in the art would expect that the activity of epothilone derivatives wherein the CO moiety at position C5 is replaced by a SO_2 moiety, and the activity of the resulting derivatives would rather be comparable with the activity of a derivative carrying an OH group at C5. As discussed above, Nicolaou teaches that this derivative shows ***a loss*** of activity.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Date: 30.08.08

Respectfully Submitted,

By: _____